National Institute on Drug Abuse
Advancing Addiction Science

**Research Report**
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# Tobacco, Nicotine, and E-Cigarettes Research Report

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# Tobacco, Nicotine, and E-Cigarettes Research Report



# Introduction

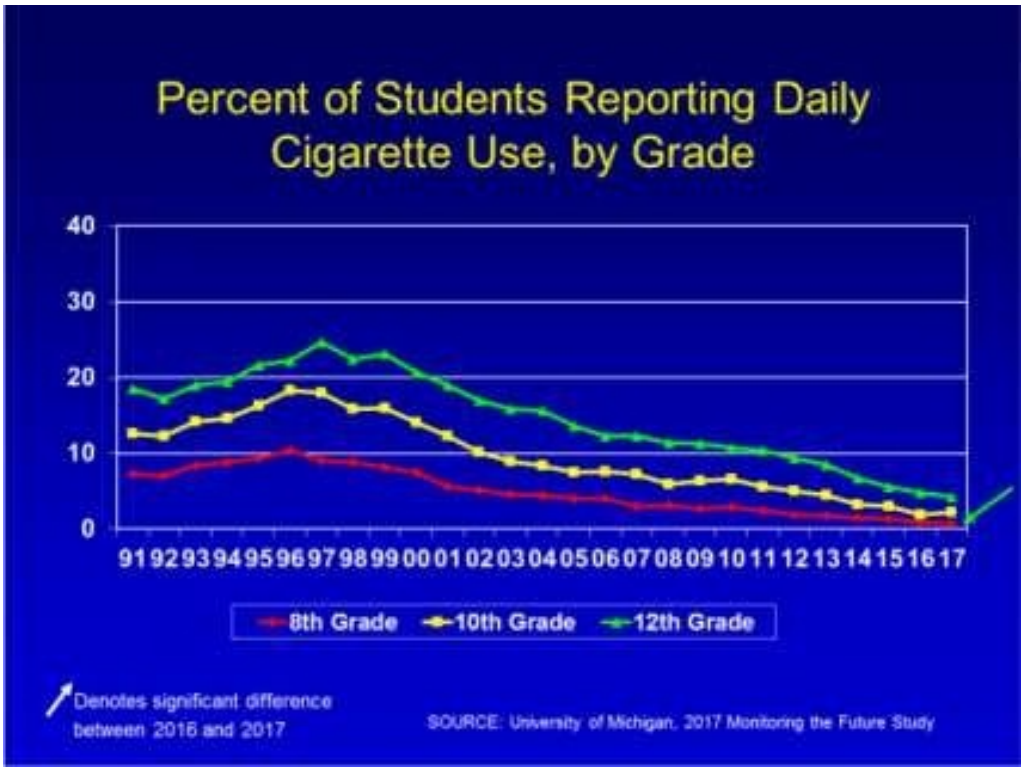
In 2014, the Nation marked the 50th anniversary of the first Surgeon General's Report on Smoking and Health. In 1964, more than 40 percent of the adult population smoked. Once the link between smoking and its medical consequences—including cancers and heart and lung diseases—became a part of the public consciousness, education efforts and public policy changes were enacted to reduce the number of people who smoke. These efforts resulted in substantial declines in smoking rates in the United States—to half the 1964 level.[1]

However, rates of cigarette smoking and other tobacco use are still too high,[2] and some populations are disproportionately affected by tobacco's health consequences. Most notably, people with mental disorders—including substance use disorders—smoke at higher rates than the general population.[3–6] Additionally, people living below the poverty line and those with low educational attainment are more likely to smoke than those in the general population. As tobacco use is the leading preventable cause of mortality in the United States,[1] differential rates of smoking and use of other tobacco products is a significant contributor to health disparities among some of the most vulnerable people in our society.

# What is the scope of tobacco use and its cost to society?

Approximately one fourth of the population uses tobacco products, and 19.4 percent smoke cigarettes. According to the 2016 National Survey on Drug Use and Health (NSDUH), an estimated 63.4 million people aged 12 or older used a tobacco product during the past month, including 51.3 million cigarette smokers.[7] Smoking rates continue to go down year to year; the percentage of people over age 18 who smoke cigarettes declined from 20.9 percent in 2005 to 15.8 percent in 2016, according to the 2017 National Health Interview Survey.

[8]




However, smoking rates are substantially higher among some of the most vulnerable people in our society. The 25 percent of Americans with mental disorders, including addiction, account for 40 percent of the cigarettes smoked in the U.S.[9] (see "Do people with mental illness and substance use disorders use tobacco more often?"). More than 40 percent of people with a General Education Development certificate (GED) smoke—which is the highest prevalence of any socioeconomic group.[10]

Also, people who live in rural areas, particularly in the South Atlantic states, use all forms of tobacco at higher rates than people who live in urban areas. These differences cannot be fully explained by different levels of poverty or affluence.[11]

Smoking among youth is at historically low levels. According to the NIDA-sponsored Monitoring the Future (MTF) survey,[12] in 2015, an estimated 4.7 million middle and high school students used tobacco products during the past month, according to data from the National Youth Tobacco Survey (NYTS)[13] e-cigarettes) were the most commonly used tobacco products among middle (5.3 percent) and high school (16.0 percent) students in 2015.[13] E-cigarettes deliver synthetic nicotine and do not

contain tobacco; however, they are classified as tobacco products for regulatory purposes. These findings are echoed by other studies,[14–17] including the MTF survey.[12] Scientists have not yet determined the medical consequences of long-term e-cigarette use or the secondhand effects of e-cigarette vapor (see "What are electronic cigarettes?").

Between 1964 and 2012, an estimated 17.7 million deaths were related to smoking[18] leads to more than 480,000 deaths annually.[1] If current smoking rates continue, 5.6 million Americans who are currently younger than 18 will die prematurely from smoking-related disease.[13]

In addition to the tremendous impact of premature deaths related to tobacco use, the economic costs are high. Experts estimate that between 2009 and 2012, the annual societal costs attributable to smoking in the United States were between $289 and $332.5 billion. This includes $132.5 to $175.9 billion for direct medical care of adults and $151 billion for lost productivity due to premature deaths. In 2006, lost productivity due to exposure to secondhand smoke cost the country $5.6 billion.[1] About 70 percent of current smokers' excess medical care costs could be prevented by quitting.[19]

# How does tobacco deliver its effects?

The smoke from combustible tobacco products contains more than 7,000 chemicals. Nicotine is the primary reinforcing component of tobacco; it drives tobacco addiction.[20,21] Hundreds of compounds are added to tobacco to enhance its flavor and the absorption of nicotine.[22] Cigarette smoking is the most popular method of using tobacco; however, many people also use smokeless tobacco products, such as snuff and chewing tobacco, which also contain nicotine (see "Other Tobacco Products"). E-cigarettes, which deliver nicotine in the absence of other chemicals in tobacco, have become popular in recent years (see "What are electronic cigarettes?").

The cigarette is a very efficient and highly engineered drug-delivery system. By inhaling tobacco smoke, the average smoker takes in 1–2 milligrams of nicotine per cigarette. When tobacco is smoked, nicotine rapidly reaches peak levels in the bloodstream and enters the brain. A typical smoker will take 10 puffs on a cigarette over the roughly 5 minutes that the cigarette is lit.[23] Thus, a person who smokes about 1 pack (20 cigarettes) daily gets 200 "hits" of nicotine to the brain each day. Among those who do not inhale the smoke—such as cigar and pipe smokers and smokeless

tobacco users—nicotine is absorbed through mucous membranes in the mouth and reaches peak blood and brain levels more slowly.

Immediately after exposure to nicotine, there is a "kick" caused in part by the drug's stimulation of the adrenal glands and resulting discharge of epinephrine (adrenaline). The rush of adrenaline stimulates the body and causes an increase in blood pressure, respiration, and heart rate.[24] Like other drugs, nicotine also activates reward pathways in the brain—circuitry that regulates reinforcement and feelings of pleasure.[20,21]

# Is nicotine addictive?

Yes. Most smokers use tobacco regularly because they are addicted to nicotine. Addiction is characterized by compulsive drug-seeking and use, even in the face of negative health consequences. The majority of smokers would like to stop smoking, and each year about half try to quit permanently. Yet, only about 6 percent of smokers are able to quit in a given year.[25] Most smokers will need to make multiple attempts before they are able to quit permanently.[22] Medications including varenicline, and some antidepressants (e.g. bupropion), and nicotine-replacement therapy, can help in many cases (see "What are treatments for tobacco dependence?").[26]

A transient surge of endorphins in the reward circuits of the brain causes a slight, brief euphoria when nicotine is administered. This surge is much briefer than the "high" associated with other drugs. However, like other drugs of abuse, nicotine increases levels of the neurotransmitter dopamine in these reward circuits,[20,21,27] which reinforces the behavior of taking the drug. Repeated exposure alters these circuits' sensitivity to dopamine and leads to changes in other brain circuits involved in learning, stress, and self-control. For many tobacco users, the long-term brain changes induced by continued nicotine exposure result in addiction, which involves withdrawal symptoms when not smoking, and difficulty adhering to the resolution to quit.[28,29]

The *pharmacokinetic* properties of nicotine, or the way it is processed by the body, contribute to its addictiveness.[24] When cigarette smoke enters the lungs, nicotine is absorbed rapidly in the blood and delivered quickly to the brain, so that nicotine levels peak within 10 seconds of inhalation. But the acute effects of nicotine also dissipate quickly, along with the associated feelings of reward; this rapid cycle causes the smoker to continue dosing to maintain the drug's pleasurable effects and prevent

withdrawal symptoms.[30]

Withdrawal occurs as a result of dependence, when the body becomes used to having the drug in the system. Being without nicotine for too long can cause a regular user to experience irritability, craving, depression, anxiety, cognitive and attention deficits, sleep disturbances, and increased appetite. These withdrawal symptoms may begin within a few hours after the last cigarette, quickly driving people back to tobacco use.

When a person quits smoking, withdrawal symptoms peak within the first few days of the last cigarette smoked and usually subside within a few weeks.[31] For some people, however, symptoms may persist for months, and the severity of withdrawal symptoms appears to be influenced by a person's genes.[30,31]

In addition to its pleasurable effects, nicotine also temporarily boosts aspects of cognition, such as the ability to sustain attention and hold information in memory. However, long-term smoking is associated with cognitive decline and risk of Alzheimer's Disease, suggesting that short-term nicotine-related enhancement does not outweigh long-term consequences for cognitive functioning.[32] In addition, people in withdrawal from nicotine experience neurocognitive deficits such as problems with attention or memory.[33] These neurocognitive withdrawal symptoms are increasingly recognized as a contributor to continued smoking.[34] A small research study also suggested that withdrawal may impair sleep for severely dependent smokers, and that this may additionally contribute to relapse.[35]

In addition to the drug's impact on multiple neurotransmitters and their receptors,[30] many behavioral factors can affect the severity of withdrawal symptoms. For many people who smoke, the feel, smell, and sight of a cigarette and the ritual of obtaining, handling, lighting, and smoking the cigarette are all associated with the pleasurable effects of smoking and can make withdrawal or craving worse.[36] Learning processes in the brain associate these cues with nicotine-induced dopamine surges in the reward system[21]—similar to what occurs with other drug addictions. Nicotine replacement therapies such as gum, patches, and inhalers, and other medications approved for the treatment of nicotine addiction may help alleviate the physiological aspects of withdrawal[37–39] (see "What are treatments for tobacco dependence?"); however, cravings often persist because of the power of these cues. Behavioral therapies can help smokers identify environmental triggers of craving so they can use strategies to avoid these triggers and manage the feelings that arise when triggers cannot be.[40,41]

### Are there other chemicals that may contribute to tobacco addiction?

Research is showing that nicotine may not be the only ingredient in tobacco that affects its addictive potential.

Smoking is linked with a marked decrease in the levels of monoamine oxidase (MAO), an important enzyme that is responsible for the breakdown of dopamine, as well as a reduction in MAO binding sites in the brain.[42] This change is likely caused by some as-yet-unidentified ingredient in tobacco smoke other than nicotine, because we know that nicotine itself does not dramatically alter MAO levels. Animal research suggests that MAO inhibition makes nicotine more reinforcing, but more studies are needed to determine whether MAO inhibition affects human tobacco dependence.[42]

Animal research has also shown that acetaldehyde, another chemical in tobacco smoke created by the burning of sugars added as sweeteners, dramatically increases the reinforcing properties of nicotine and may also contribute to tobacco addiction.[43]

## What are the physical health consequences of tobacco use?

Cigarette smoking harms nearly every organ in the body,[1,44] and smoking is the leading preventable cause of premature death in the United States. Although rates of smoking have declined, it is estimated that it leads to about 480,000 deaths yearly.[1] Smokers aged 60 and older have a twofold increase in mortality compared with those who have never smoked, dying an estimated 6 years earlier.[45]

Quitting smoking results in immediate health benefits, and some or all of the reduced life expectancy can be recovered depending on the age a person quits.[46]

Although nicotine itself does not cause cancer, at least 69 chemicals in tobacco smoke are carcinogenic,[1] and cigarette smoking accounts for at least 30 percent of all cancer deaths.[22] The overall rates of death from cancer are twice as high among smokers as nonsmokers, with heavy smokers having a four times greater risk of death from cancer than nonsmokers.[1]

Foremost among the cancers caused by tobacco use is lung cancer. Cigarette smoking has been

linked to about 80 to 90 percent of all cases of lung cancer, the leading cause of cancer death for both men and women, and it is responsible for roughly 80 percent of deaths from this disease.[22,47] Smoking increases lung cancer risk five to tenfold, with greater risk among heavy smokers.[48] Smoking is also associated with cancers of the mouth, pharynx, larynx, esophagus, stomach, pancreas, cervix, kidney, and bladder, as well as acute myeloid.[1] Cigarette smoking is not the only form of tobacco use associated with cancers. Smokeless tobacco (see "Other Tobacco Products") has been linked to cancer of the pharynx, esophagus, stomach, and lung, as well as to colorectal cancer.[49]

In addition to cancer, smoking causes lung diseases such as chronic bronchitis and emphysema, and it has been found to exacerbate asthma symptoms in adults and children. Cigarette smoking is the most significant risk factor for chronic obstructive pulmonary disease (COPD).[50] Survival statistics indicate that quitting smoking results in repair to much of the smoking-induced lung damage over time. However, once COPD develops, it is irreversible; COPD-related lung damage is not repaired with time.

Smoking also substantially increases the risk of heart disease, including stroke, heart attack, vascular disease, and aneurysm.[51,52] Cardiovascular disease is responsible for 40 percent of all smoking-related deaths.[53] Smoking causes coronary heart disease, the leading cause of death in the United States. Smoking is also linked to many other major health conditions—including rheumatoid arthritis, inflammation, and impaired immune function.[1] Even young smokers aged 26 to 41 report reduced health-related quality of life compared with nonsmoking peers, according to a cross-sectional population study.[54] Recent animal research also identified a pathway between the pancreas and a part of the brain active in nicotine intake, potentially linking cigarette smoking to the risk of developing Type 2 Diabetes.

# What are the effects of secondhand and thirdhand tobacco smoke?

Secondhand smoke is a significant public health concern and driver of smoke-free policies. Also called passive or secondary smoke, secondhand smoke increases the risk for many diseases.[55] Exposure to environmental tobacco smoke among nonsmokers increases lung cancer risk by about

20 percent.[48] Secondhand smoke is estimated to cause approximately 53,800 deaths annually in the United States.[55] Exposure to tobacco smoke in the home is also a risk factor for asthma in children.[56]

Smoking also leaves chemical residue on surfaces where smoking has occurred, which can persist long after the smoke itself has been cleared from the environment. This phenomenon, known as "thirdhand smoke," is increasingly recognized as a potential danger, especially to children, who not only inhale fumes released by these residues but also ingest residues that get on their hands after crawling on floors or touching walls and furniture. More research is needed on the risks posed to humans by thirdhand smoke, but a study in mice showed that thirdhand smoke exposure has several behavioral and physical health impacts, including hyperactivity and adverse effects on the liver and lungs.[57]

## What are the risks of smoking during pregnancy?

Smoking during pregnancy is linked with a range of poor birth outcomes—including:

- Low birth weight and preterm birth[58,59]
- Restricted head growth[60]
- Placental problems[61]
- Increased risk of still birth[62]
- Increased risk of miscarriage[62,63]

Health and developmental consequences among children have also been linked to prenatal smoke exposure, including:

- Poorer lung function, persistent wheezing, and asthma, possibly through DNA methylation[64]
- Visual difficulties, such as strabismus, refractive errors, and retinopathy[65]

Photo by morgueFile.com

Unfortunately, smoking by pregnant women is common. In 2014, 8.4 percent of women smoked at any time during pregnancy, with those aged 20 to 24 who were American Indian or Alaska Natives having higher rates, at 13 percent and 18 percent, respectively.[66] One fifth of women who smoked during the first 6 months of pregnancy quit by their third trimester. Overall cessation rates were highest for those with the highest educational attainment and private insurance.[66] Therefore, there is a clear need to expand smoking cessation treatment to younger women and to those of lower

socioeconomic status (see Box: "Smoking Cessation for Pregnant Women").

# How many adolescents use tobacco?

Photo by NIDA

Most people who use tobacco started during adolescence, and those who begin at a younger age are more likely to develop nicotine dependence and have trouble quitting.[67] According to the 2017 Monitoring the Future Survey, 9.7 percent of 12th graders, 5.0 percent of 10th graders, and 1.9 percent of 8th graders used cigarettes in the past month.[12] Analyses of the 2012 National Youth Tobacco Survey (NYTS) found that 20.8 percent of current adolescent tobacco users reported wanting to use tobacco within 30 minutes of waking—a classic symptom of nicotine dependence. This study also found that 41.9 percent reported strong cravings for tobacco.[68] Other research has found that light and intermittent smoking among adolescents is associated with the same level of difficulty quitting as daily smoking.[69]

Any exposure to nicotine among youth is a concern. The adolescent brain is still developing, and nicotine has effects on the brain's reward system and brain regions involved in emotional and cognitive functions.[70] Research suggests that the nicotine-related changes to these areas of the brain during adolescence may perpetuate continued tobacco use into adulthood.[71] These changes also contribute to a higher rate of other substance use disorders among people who use tobacco during adolescence, sometimes referred to as a "gateway" effect.[70,72]

Mental health, beliefs about smoking, perception of schoolmates' smoking, and other substance use are additional factors that can influence an adolescent's risk for smoking and nicotine dependence.[73] Emotional problems—including depression[74] and recent negative life events[75]—are associated with tobacco use among adolescents. Smoking among peers and within social groups is a major environmental factor that influences adolescent smoking; social smoking is a more important motivator for adolescents compared to adult smokers.[76]

Photo by Mandie Mills, CDC

It is common for adolescent smoking to follow an intergenerational pattern, which has genetic, epigenetic, and environmental influences.[73,77] Data from parents and adolescents suggests that current parental nicotine dependence is strongly linked with adolescent smoking and dependence. Other factors—such as parents' education, marital status, and parenting behavior also influence teen smoking.

# What are electronic cigarettes?

E-cigarettes (electronic nicotine delivery systems) emerged in the U.S. market in 2007 and have rapidly grown in popularity.[78] E-cigarettes, or e-vaporizers, are devices that heat a liquid containing solvents, flavors, and often nicotine.[79] Users inhale the resulting vapor. A variety of designs are available, some mimicking the look of traditional cigarettes. More than 7,000 flavors are available for e-cigarettes,[80] some of which are especially appealing to youth. Many convenience stores, drug

stores, grocery stores, and other physical and online retail outlets sell e-cigarettes, although as of mid December, 2019, it is illegal to sell any nicotine or tobacco products to people under 21.[237] Some convenience stores and drugstore chains have also stopped selling e-cigarettes to promote public health.

In 2013, more than one third of cigarette smokers said they had ever used e-cigarettes.[78] According to data from the 2014 Tobacco Products and Risk Perceptions Survey, current cigarette smokers had a greater likelihood of using e-cigarettes. This analysis found that half of cigarette smokers had ever used an e-cigarette and 20.7 percent currently used these devices. However, approximately 10 percent of adults who used e-cigarettes had never smoked previously.[81] Data from the 2014 National Health Interview Survey indicated that 0.4 percent of adults who have never smoked and 0.8 percent of former smokers (abstinent 4 or more years) currently use e-cigarettes.[82] The survey also found that 13 percent of daily e-cigarette users were former smokers who quit during the past year.[82]

As with cigarette use, e-cigarette use is higher among people with mental health conditions—with 3.1 percent currently using compared with 1.1 percent of those without mental illness.[83] It is also a concern that pregnant women are using e-cigarettes, as nicotine exposure during periods of developmental vulnerability (including prenatal development) has adverse health consequences.[84]

Users report the belief that e-cigarette products are less harmful than traditional cigarettes,[85] and many report using them to help quit smoking traditional cigarettes. While it is not yet clear if e-cigarettes are effective smoking cessation aids, the devices are sometimes marketed for this purpose[86] (see "Are e-cigarettes useful for smoking cessation?"). Some research suggests that older adults use these devices as a tobacco substitute, although not always as a cessation method.[87] Users also cite convenience and being conscientious towards others as reasons for using these products.[88]

## Reports of Deaths Related to Vaping

The Food and Drug Administration has alerted the public to thousands of reports of serious lung illnesses associated with vaping, including dozens of deaths. They are working with the Centers for Disease Control and Prevention (CDC) to investigate the cause of these illnesses. Many of the suspect products tested by the states or federal health officials have been identified

as vaping products containing THC, the main psychotropic ingredient in marijuana. Some of the patients reported a mixture of THC and nicotine, and some reported vaping nicotine alone. No one substance has been identified in all of the samples tested, and it is unclear if the illnesses are related to one single compound. Until more details are known, FDA officials have warned people not to use any vaping products bought on the street, and they warn against modifying any products purchased in stores. They are also asking people and health professionals to report any adverse effects. The CDC has posted an information page for consumers.

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## How does the federal government regulate e-cigarettes?

The U.S. Food and Drug Administration (FDA), which regulates cigarettes, tobacco, and smokeless tobacco, gained the authority in 2016 to also regulate electronic nicotine delivery systems (such as e-cigarettes and vape pens), all cigars, hookah (waterpipe) tobacco, pipe tobacco, and nicotine gels, among other tobacco products. Under the new regulations, e-cigarette manufacturers must list ingredients. *In December 2019, the federal government raised the legal minimum age of sale of tobacco products from 18 to 21 years, and in January 2020, the FDA issued a policy on the sale of flavored vaping cartridges*

Is it true that e-cigarettes are safer than traditional cigarettes?

It is likely that, on balance, e-cigarettes are safer than traditional cigarettes from the standpoint of physical health. However, as discussed above, the nicotine in e-cigarettes can cause addiction and neurocognitive impairments.

Although for regulatory purposes e-cigarettes are classified as “tobacco products,” they do not contain tobacco or produce the same toxic combustion products, like tar, that cause lung cancer and other diseases in users and people exposed to secondhand smoke. However, the vapor from e-cigarettes typically contains nicotine and a range of other chemicals.[89] Because these products are relatively new, evidence on the short-term effects of exposure to e-cigarette aerosols is limited, and very little is known about the long-term health effects.

A review of recent literature found that some of the chemicals in e-cigarette liquid, propylene glycol and glycerol, cause throat irritation and coughing.[89] Other research suggests that vapor exposure may be linked with impaired lung function.[89] Chemical analyses that compare the profiles of electronic and traditional cigarettes have suggested that e-cigarettes have a reduced carcinogenic profile and impart a lower potential for disease.[90] However, toxicants, carcinogens, and metal particles have been detected in the liquids and aerosols of e-cigarettes, and it is currently unclear what risk they pose with repeated use.[91] As with traditional cigarettes, use of e-cigarettes involuntarily exposes nonusers to secondhand and thirdhand aerosol.[91]

The research on secondhand exposure to the aerosol from e-cigarettes is limited, but one study found that fine particulate matter concentrations during an indoor event in a large room with e-cigarette smokers were higher than those reported previously in venues that allowed cigarette smoking.[88] An in vitro study showed that exposing lung tissues and cells to e-cigarette liquid induced increased inflammatory responses and oxidative stress markers.[92] Another study that analyzed e-cigarette flavorings found that 39 of the 51 flavors tested positive for diacetyl, a chemical associated with an irreversible obstructive lung disease called bronchiolitis obliterans. Other chemicals, 2,3-pentanedione and acetoin, associated with severe respiratory diseases among exposed people, were also found in many e-cigarette flavorings.[89]

The amount of nicotine in e-cigarette fluid varies. Some research has found that e-cigarettes

deliver less nicotine on average than traditional cigarettes,[93] but that users may change puffing patterns to compensate. Inexperienced e-cigarette users take in modest nicotine concentrations, but those who regularly use these devices adjust their puffing to consume similar levels of the drug as with traditional cigarettes.[93–95] Newer e-cigarette devices can deliver substantial amounts of nicotine, and some users are able to get nicotine at levels similar to[96] or even greater than a traditional cigarette.[97,98] One study found equivalent levels of nicotine's major metabolite in the blood of smokers who use traditional and e-cigarettes.[89] Thus, all the nicotine-related concerns of traditional cigarettes—addiction, effects on cognitive function, and effects on prenatal development—apply to e-cigarettes as well.

## Risks of E-Cigarettes to Children

Young children may accidentally ingest the concentrated nicotine (which often contains flavors) in e-cigarette liquid.[91] The Centers for Disease Control and Prevention recently compared calls to poison centers in the United States related to human exposures to e-cigarettes and traditional cigarettes. The study found that between September 2010 and February 2014, the proportion of e-cigarette calls among all cigarette-related calls increased from 0.3 percent to 41.7 percent.[99] Most of the e-cigarette exposures were among children under the age of 5 years (51.1 percent) and people over age 20 (42.0 percent), whereas almost all traditional cigarette exposure calls involved young children.[99] Data indicated that a greater proportion of e-cigarette exposure calls (57.8 percent) resulted in adverse health effects than traditional cigarette exposure (36.0 percent). These adverse health effects included vomiting, nausea, and eye irritation.[99]

Are e-cigarettes useful for smoking cessation?

Some research suggests e-cigarettes may help people quit smoking cigarettes, while other data suggest that they can impede quitting and that they may open the door to traditional cigarette use for people who might not otherwise try them. Thus, much more research is needed on this question.

One review of recent studies suggested that the likelihood of quitting cigarettes was 28 percent lower among individuals who used e-cigarettes compared with those who did not use these devices, regardless of whether users were interested in quitting.[100] Research from the United Kingdom suggests that among smokers who continue to use traditional cigarettes, daily use of e-cigarettes was associated with increased attempts to quit and cut back, but not with success.[101] However, another analysis estimated that, in England, 16,000 smokers were able to quit in 2014 who would not have quit if e-cigarettes had not been available.[102] A review and meta-analysis also suggested that using e-cigarettes for a minimum of 6 months was associated with quitting or reducing the number of cigarettes used.[103]

## E-cigarettes and Teens

National survey data suggest that e-cigarettes were the most commonly used nicotine delivery product among youth.[12–17] A review of the literature found that up to 20 percent of adolescents who currently use e-cigarettes had never smoked a traditional cigarette.[87]

A major concern is that e-cigarettes' flavors, design, and marketing particularly appeal to youth,[91] and that by introducing young people to nicotine and glamorizing a smoking-like behavior, e-cigarettes could open the door to cigarette use in a population that is particularly vulnerable to addiction and that has seen historic declines in cigarette smoking.

Some research indicates that e-cigarette use may lead to the use of traditional cigarettes among adolescents and young adults.[104] According to data from the 2012 NYTS, youth who had only used e-cigarettes reported an increased intention to smoke traditional cigarettes compared with peers who had never used these devices. The survey found no link between e-cigarette use and intention to quit smoking among youth who were current smokers, indicating that this age group

does not see these products primarily as smoking-cessation aids.[105] A longitudinal cohort study of 16- to 26-year-olds who had never smoked traditional cigarettes found that 2.3 percent (16 participants) used e-cigarettes at the start of the study. After a one-year follow-up, approximately 69 percent (11 of 16) of these participants progressed to smoking traditional cigarettes compared to 18.9 percent (128 of 678) among those who never used an e-cigarette.[106]

Another study found that past-month e-cigarette use predicted future cigarette use, but that past-month cigarette use did not predict future e-cigarette use.[107]

Many young people report experimenting with e-cigarettes out of curiosity, because the flavors appeal to them, or because of peer influences.[108] The majority of youth who reported e-cigarette use in one study had friends who used these products. Almost half of adolescents who used e-cigarettes said that they did not believe these products were associated with health risks.[109] Young people also perceived e-cigarettes as easy to obtain, "cool," and a better alternative to cigarettes because they were thought to be healthier and could be used anywhere. Among youth who stopped using e-cigarettes, the major underlying reasons were health concerns, loss of interest, high cost, bad taste, and view of e-cigarettes as less satisfying than cigarettes.[108]

# Other Tobacco Products

While cigarette smoking has declined significantly during the past 40 years, use of other tobacco products is increasing—particularly among young people.[110] These include:

- **Cigars:** tobacco wrapped in leaf tobacco or another tobacco-containing substance instead of paper, which can be bought individually
- **Cigarillos:** small cigars that cost less and are also available for purchase individually
- **Hookahs or waterpipes:** pipes with a long, flexible tube for drawing smoke from lit, flavored tobacco through water contained in a bowl
- **Smokeless tobacco:** products like chewing tobacco and snuff that are placed in the mouth between the teeth and gums

- **Powder tobacco:** mixtures that are inhaled through the nose

In 2014, almost one-quarter of high school students reported past-month use of a tobacco product—with e-cigarettes (13.4 percent), hookahs (9.4 percent), cigarettes (9.2 percent), cigars (8.2 percent), smokeless tobacco (5.5 percent), and snus (moist powder tobacco) (1.9 percent) as the most popular.[17]

## Cigars

In 2016, an estimated 12 million people aged 12 or older (4.6 percent of the adolescent and adult population) smoked cigars during the past month.[7] The majority of adolescents and young adults who smoked cigars also smoke cigarettes.[111]

## Cigarillos

Data from the Tobacco Use Supplement to the Current Population Survey and NSDUH suggest that younger and less economically advantaged males initiate tobacco use with cigarillos.[111] From 2002 to 2011, past-month cigarette smoking declined for males and females of all age groups. However, during this same period, rates of cigarillo use among males aged 18 to 25 remained constant (at approximately 9 percent).[111]

## Hookahs or waterpipes

Between 2011 and 2014, use of hookah increased among middle and high school students, despite decreased use of cigarettes and cigars, according to the NYTS.[17] Research also suggests that rates of hookah use for tobacco smoking increase during the first month of college.[112] Nationally representative data from college students indicate that daily cigarette or cigar smokers (as well as marijuana users) were more likely to be frequent waterpipe users.[113]

Hookah users may mistakenly believe that it is less addictive or dangerous than cigarettes; however, one session of hookah smoking exposed users to greater smoke volumes and higher levels of tobacco toxicants (e.g., tar) than a single cigarette.[114] Additionally, hookah smoking is linked with nicotine dependence and its associated medical consequences[115,116] (see "What are the physical health consequences of tobacco use?"). Reviews of the literature on waterpipe users suggest that like those who use other forms of tobacco, many have tried to quit but have been unsuccessful on their

own.[115] These findings indicate the need for tobacco control policies and prevention and treatment interventions for this form of nicotine delivery that are similar to those seen for cigarettes.

## Smokeless tobacco

In 2016, 8.8 million people aged 12 or older (3.3 percent of this population) used smokeless tobacco during the past month.[7] Overall, use of smokeless tobacco among adults decreased from 1992 to 2003 but has held constant since.[117] Longitudinal data suggest that people are more likely to switch from smokeless tobacco use to cigarette smoking than vice versa.[118] Although smokers may attempt to use smokeless products to cut down or quit, research suggests that this approach is not effective.[116] However, some argue that using smokeless tobacco in lieu of cigarettes may help reduce the harms associated with smoking traditional cigarettes.[119]

## Polytobacco Use

Some users of tobacco consume it in multiple forms (polytobacco use); this behavior is associated with greater nicotine dependence[120] and the risk for other substance use disorder.[72] Analyses of a decade of data from NSDUH found steady rates of polytobacco use from 2002 to 2011 (8.7 percent to 7.4 percent) among people age 12 and older. However, use of some product combinations—such as cigarettes and smokeless tobacco, cigars and smokeless tobacco, and use of more than two products—increased over that period.[120]

Among individuals younger than 26, rates of polytobacco use increased despite declines in overall tobacco use. Polytobacco use was associated with being male, having relatively low income and education, and engaging in risk-taking behaviors.[120] In 2014, an estimated 2.2 million middle and high school students had used two or more types of tobacco products during the past month, according to the NYTS.[121] Polytobacco use was common, even among students who used tobacco products 5 days or fewer during the past month.[121] The 2012 NYTS had found that 4.3 percent of students used three or more types of tobacco. This study also observed that male gender, use of flavored products, nicotine dependence, receptivity to tobacco marketing, and perceived peer use were all associated with youth polytobacco use.[122]

### Flavored Tobacco Use Among Adolescents and Young Adults

One specific concern about e-cigarettes and tobacco products like cigarillos and hookahs is the addition of flavorings, which may make them particularly appealing to youth.[17,111] The Family Smoking Prevention and Tobacco Control Act of 2009 banned the sale of cigarettes with flavors other than menthol, but other flavored tobacco products (e.g., small cigars, cigarillos, and smokeless tobacco) can still be sold. Adding flavors to tobacco products or to the nicotine solution of e-cigarettes can make them more appealing to some users because they can mask the harsh taste.[108,123] Although more research is needed on how flavors affect long-term use, health experts have expressed concerns that many of the flavorings used in tobacco products are also found in candies and beverages.[124] Such flavors may make them more appealing to youth and may contribute to increased use of these products among young people.

Approximately 6.3 percent of middle and high school students reported using either flavored cigarettes or small cigars, according to the 2011 NYTS.[125] Data from the 2014 NYTS indicate that of middle and high school students who currently used tobacco, about 70 percent—an estimated 3.26 million youths—had used at least one flavored tobacco product during the past month.[126] Among past-month users, the most commonly used flavored products were e-cigarettes, hookah tobacco, and cigars.[126] It seems that youth may not necessarily “grow out of” using flavored tobacco products. Among young adults aged 18 to 34, nearly one-fifth (18.5 percent) of those who use tobacco, consumed flavored (including menthol) products.[127]

# Are there gender differences in tobacco smoking?

Generally, men tend to use all tobacco products at higher rates than women.[128] In 2015, 16.7 percent of adult males and 13.6 percent of adult females smoked cigarettes.[129] Such differences may relate to a combination of physiological (particularly ovarian hormones), cultural, and behavioral factors.[130]

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Results from neuroimaging studies suggest that smoking activates men's reward pathways more than women's.[131] This finding is consistent with the idea that men smoke for the reinforcing effects of nicotine, whereas women smoke to regulate mood or in response to cigarette-related cues. A study of stress responses and craving among male and female smokers who were trying to quit found that during abstinence, lower levels of the stress hormone cortisol predicted relapse in men. However, high cortisol levels were predictive of relapse in women.[132] Other work on abstinence found that smoking a cigarette with nicotine, as compared to a de-nicotinized cigarette, alleviated the symptoms of withdrawal and negative mood to a greater extent in men than women. Women obtained equal relief from cigarettes with and without nicotine, suggesting that they found the drug less rewarding than men.[133]

Cigarette craving is a major reason why smokers find it hard to quit, and this strong urge to smoke can be evoked by sensory cues and stress. Research suggests that women experience stronger craving than men in response to stress,[134] but men may be more responsive to environmental cues.[135] Additionally, longitudinal data from international surveys conducted in four industrialized countries indicated that men and women did not differ in their desire to quit, plans to quit, or quit attempts. However, women were 31 percent less likely to quit successfully.[136] One reason why women may have difficulty quitting is post-cessation weight gain. This concern should be addressed in behavioral counseling and adjunct treatments for all smokers.[137]

The overall lower cessation rate for women may reflect sex differences in response to particular medications (see "What are treatments for tobacco dependence?"). For example, varenicline has greater short- and immediate-term efficacy (at 3 and 6 months) among women smokers. However, women and men show similar 1-year quit rates when using varenicline.[138] In contrast, a combination of varenicline plus bupropion was less effective for cessation among women compared with men.[139]

Another particular concern related to tobacco use among women is smoking during pregnancy (see "What are the risks of smoking during pregnancy?").

# Do people with mental illness and substance use disorders use tobacco more often?

There is significant comorbidity between tobacco use and mental disorders. People with mental illness smoke at two to four times the rate of the general population. Among people with a mental illness, 36.1 percent smoked from 2009 to 2011, compared with 21.4 percent among adults with no mental illness.[140] Smoking rates are particularly high among patients with serious mental illness (i.e., those who demonstrate greater functional impairment). While estimates vary, as many as 70-85 percent of people with schizophrenia and as many as 50-70 percent of people with bipolar disorder smoke.[141,142]

Rates of smoking among people with mental illness were highest for those younger than 45, those with low levels of education, and those living below the poverty level.[143] Longitudinal data from NSDUH (2005–2013) indicate that smoking among adults without chronic conditions has declined significantly, but remains particularly high among those reporting anxiety, depression, and substance use disorders.[3] Smoking is believed to be more prevalent among people with depression and schizophrenia because nicotine may temporarily lessen the symptoms of these illnesses, such as poor concentration, low mood, and stress.[144–146] But it is important to note that smoking cessation has been linked with improved mental health—including reduced depression, anxiety, and stress, and enhanced mood and quality of life.[147]

Analyses of longitudinal NSDUH data also found a higher prevalence of smokeless tobacco use among individuals with mental health and substance use disorders.[3] Other research drawing on data

from the National Epidemiologic Survey on Alcohol and Related Conditions found that all types of substance dependence were associated with dependence on nicotine.[148] Smoking is also highly prevalent among people in treatment for substance use disorders,[149] with most studies finding rates between 65-85 percent among patients in addiction treatment.[149]

Additionally, smokers with a mental health disorder tend to smoke more cigarettes than those in the general population. The average number of cigarettes smoked during the past month was higher among those with a mental illness compared with those without one—331 versus 310 cigarettes.[150] High cigarette consumption is a particular problem for people with serious mental illness. Although adults with serious mental illness comprised only 6.9 percent of past-month smokers, they consumed 8.7 percent of all cigarettes sold, according to data from the 2008–2012 NSDUH.[151]

### High Prevalence of Smoking Among People with Schizophrenia

Researchers are working to identify the brain circuits that contribute to the high prevalence of smoking among people with schizophrenia. Schizophrenia is associated with widespread reductions in functional connectivity between the dorsal anterior cingulate cortex and diverse parts of the limbic system. One report identified 15 circuits for which the reduction of functional connectivity correlated with severity of nicotine addiction.[152]

People with mental and substance use disorders do not quit smoking at the same rate as those in the general population.[4] Survey responses from people who have smoked at some point during their lives indicated that fewer smokers with mental illness had quit compared to those without psychiatric disorders: 47.4 percent of lifetime smokers without mental illness smoked during the past month, compared with 66 percent of those with mental illness.[150] Having a mental disorder at the time of cessation is a risk factor for relapse to smoking, even for those who have sustained abstinence for more than a year.[153] Many smokers with mental illness want to quit for the same reasons cited by others (such as health and family), but they may be more vulnerable to relapse related to stress and negative feelings.[154]

The disparity in smoking prevalence is costing lives. A recent study found that tobacco-related diseases accounted for approximately 53 percent of deaths among people with schizophrenia, 48

percent among those with bipolar disorder, and 50 percent among those with depression.[155]

Since the 1980s, many providers have believed that people with schizophrenia smoke to obtain relief from symptoms like poor concentration, low mood, and stress.[147] But research is now showing that smoking is associated with worse behavioral and physical health outcomes in people with mental illness, and quitting smoking is showing clear benefits for this population.[147,156] Comprehensive tobacco control programs and enhanced efforts to prevent and treat nicotine addiction among those with mental illness would reduce illness and deaths. Integrated treatment—concurrent therapy for mental illness and nicotine addiction—will likely have the best outcomes.[157]

Smokers who receive mental health treatment have higher quit rates than those who do not.[6] Moreover, evidence-based treatments that work in the general population are also effective for patients with mental illness. For example, people with schizophrenia showed better quit rates with the medication bupropion, compared with placebo, and showed no worsening of psychiatric symptoms.[158,159]

A combination of the medication varenicline and behavioral support has shown promise for helping people with bipolar and major depressive disorders quit, with no worsening of psychiatric symptoms.[160] A clinical trial found that a combination of varenicline and cognitive behavioral therapy (CBT) was more effective than CBT alone for helping people with serious mental illness stop smoking for a prolonged period—after 1 year of treatment and at 6 months after treatment ended.[161]

# What are treatments for tobacco dependence?

There are effective treatments that support tobacco cessation, including both behavioral therapies and FDA-approved medications. FDA-approved pharmacotherapies include various forms of nicotine replacement therapy as well as bupropion and varenicline. Research indicates that smokers who receive a combination of behavioral treatment and cessation medications quit at higher rates than those who receive minimal intervention.[37,40,162–167] Interventions such as brief advice from a health care worker, telephone helplines, automated text messaging, and printed self-help materials can also facilitate smoking cessation.[163]

Cessation interventions utilizing mobile devices and social media also show promise in boosting tobacco cessation.[168] It is important for cessation treatment to be as personalized as possible, as some people smoke to avoid negative effects of withdrawal while others are more driven by the rewarding aspects of smoking.

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### Surgeon General's Report on Smoking Cessation

The Surgeon General's Report on Smoking Cessation, released in January 2020, offers evidence that smoking cessation is beneficial at any age, improves health status and enhances quality of life. It also reduces the risk of premature death and can add as much as a decade to life expectancy.

The prevalence of tobacco use and dependence among adolescents—as well as the neurobiological impact and medical consequences of nicotine exposure—suggest that pediatric primary care settings should deliver tobacco cessation treatments to both youth and parents who use tobacco.[169] Current clinical guidance does not recommend medications for adolescent tobacco cessation because of a lack of high-quality studies;[170] however, a combination of behavioral treatments—such as motivational enhancement and CBT—has shown promise for helping adolescents quit tobacco.[171] More well-designed smoking cessation studies need to be conducted with adolescent smokers, particularly in the area of pharmacologic treatments for nicotine dependence.[170]

## Behavioral Treatments

Behavioral counseling is typically provided by specialists in smoking cessation for four to eight sessions.[40] Both in-person and telephone counseling have been found beneficial for patients who are also using cessation medications.[164] A variety of approaches to smoking cessation counseling are available.

**Cognitive Behavioral Therapy (CBT)**—CBT helps patients identify triggers—the people, places, and things that spur behavior—and teaches them relapse-prevention skills (e.g., relaxation techniques) and effective coping strategies to avoid smoking in the face of stressful situations and triggers.[172,173] A study that compared CBT and basic health education observed that both interventions reduced nicotine dependence.[174] However, another study found that among smokers trying to quit with the nicotine replacement therapy (NRT) patch, patients who participated in six sessions of intensive group CBT had better quit rates than those who received six sessions of general health education.[175]

**Motivational Interviewing (MI)**—In MI, counselors help patients explore and resolve their ambivalence about quitting smoking and enhance their motivation to make healthy changes. MI is

patient-focused and nonconfrontational, and providers point out discrepancies between patients' goals or values and their current behaviors. They adjust to patients' resistance to change and support self-efficacy and optimism.[173] Studies of MI suggest that this intervention results in higher quit rates than brief advice to stop smoking or usual care.[176]

**Mindfulness**—In mindfulness-based smoking cessation treatments, patients learn to increase awareness of and detachment from sensations, thoughts, and cravings that may lead to relapse.[177] In this therapy, patients purposely attend to the thoughts that trigger cravings and urges for tobacco and cognitively reframe them as expected and tolerable. Patients learn techniques that help them tolerate negative emotions—including stress and cravings—without returning to tobacco use or other unhealthy behaviors.[177] Interest in mindfulness-based treatments has increased during the past decade, and studies show that this approach benefits overall mental health and can help prevent relapse to smoking.[178] However, well-controlled clinical trials are needed.

**Telephone support and quitlines**—As part of tobacco control efforts, all states offer toll-free telephone numbers (or quitlines) with smoking cessation counselors who provide information and support (800-QUIT-NOW or 800-784-8669). Studies of quitline interventions indicate that smokers who call quitlines benefit from these services,[179] particularly when a counselor calls them back for multiple sessions.[180] There is limited evidence on the optimal number of calls needed, but smokers who participated in three or more calls had a greater likelihood of quitting, compared with those who only received educational materials, brief advice, or pharmacotherapy alone.[180] Quitlines have also been shown to help smokeless tobacco cessation.[181] The U.S. Department of Health and Human Services provides a Smoking Quitline (877-44U-QUIT or 877-448-7848), as well as more information and tools for quitting (including text messages and other telephone-based support) at https://smokefree.gov/.

**Text messaging, web-based services, and social media support**—Technology, including mobile phones, internet, and social media platforms can be used to provide smoking cessation interventions. These technologies have the power to increase access to care by extending the work of counselors and overcoming the geographical barriers that may deter people from entering treatment.

A review of the literature on technology-based smoking cessation interventions (internet, personal computer, and mobile telephone) found that these supports can increase the likelihood of adults

quitting, compared with no intervention or self-help information, and they can be a cost-effective adjunct to other treatments.[182] A technology does not necessarily have to be recent or highly sophisticated to help boost cessation rates. For example, studies suggest that adults who receive encouragement, advice, and quitting tips via text-message—a capability on even the most basic mobile devices—show improved quit rates compared with control programs.[183,184]

Among adult tobacco users who called a state quitline, most selected an integrated phone/web cessation program in favor of a web-only intervention.[185] Participants who chose the web-only option tended to be younger and healthier smokers, with a higher socioeconomic status. These participants tended to interact intensely with the site once, but did not re-engage as much as those who opted for the phone/web combination. A review of internet-based smoking cessation programs for adults suggested that interactive internet-based interventions that are tailored to individual needs can help people quit for 6 months or longer.[186,187] Future research should determine the effectiveness of different technologies for smoking cessation support among populations that may be hard to reach, including those of low socioeconomic status and adults older than age 50.

Technology-based cessation interventions are particularly relevant to young adults aged 18 to 25—about 3.2 million of whom smoked daily in 2016.[7] A systematic review and meta-analysis of published randomized trials of technology-based interventions—including computer programs, internet, telephone, and text messaging—for smoking cessation among this population found that they increased abstinence by 1.5 times that of comparison subjects.[188] Researchers recommend embedding cessation interventions in commonly used social networking platforms,[189] and there has been some exploratory work in this area. Results of a trial with a relatively small number of participants suggested that Facebook was an accessible, low-cost platform for engaging young adults considering cessation. However, the study pointed to challenges in maintaining participation, retaining young people in the program, and the need for gender-specific features.[189] A randomized controlled trial has been designed to test a stage-based smoking cessation intervention on Facebook tailored for smokers aged 18 to 25. Participants will be recruited online, randomly assigned to a Facebook group according to their readiness to quit, and will receive tailored daily messages and weekly counseling. The study will assess the intervention's impact on abstinence from smoking 3, 6, and 12 months after treatment, number of cigarettes smoked, quit attempts lasting 24 hours or more, and commitment to abstinence.[190]

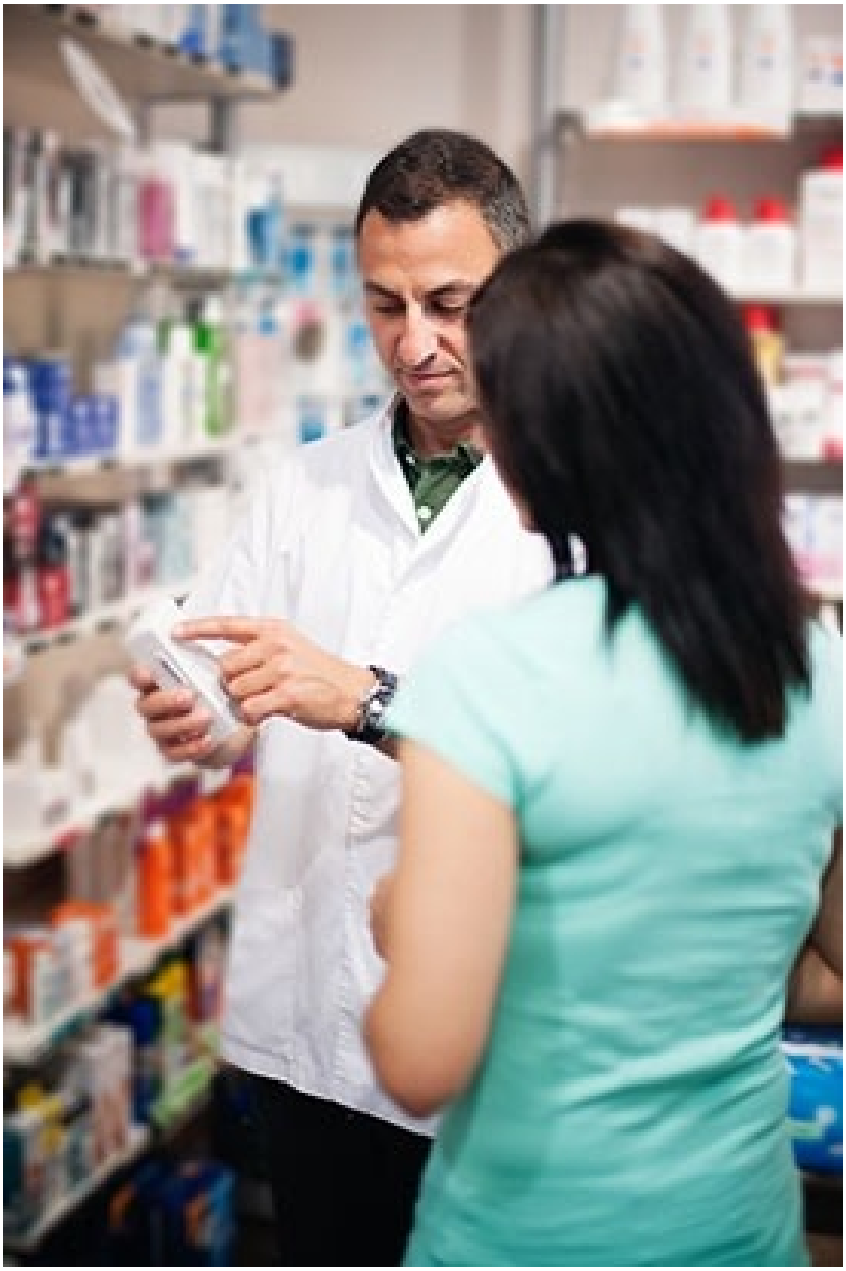
## Smoking Cessation for Pregnant Women

Given the risks associated with smoking during pregnancy, but also the challenges faced by all smokers when trying to quit, researchers have studied an array of approaches to improve cessation rates for this population. Many women are motivated to quit during pregnancy, but like other smokers, most will need assistance.

Studies show that behavioral treatments are effective, whereas pharmacotherapies have only marginal success.[191] A combination of incentives and behavioral counseling is most effective for pregnant women.[192] Adding vouchers to routine care (which included free nicotine replacement therapy for 10 weeks and four weekly support phone calls) more than doubled cessation rates during pregnancy.[193] Pooled results of behavioral intervention studies indicate that treatment reduced preterm births and the proportion of infants born with low birth weight, compared with usual care.[194] This finding is supported by an analysis of pooled results from studies with economically disadvantaged pregnant smokers, which found that voucher-based incentives improved sonographically estimated fetal growth, birth weight, percentage of low-birth-weight deliveries, and breastfeeding duration.[195,196]

# Medications

**Nicotine Replacement Therapy (NRT)**—A variety of formulations of nicotine NRTs are available over the counter—including the transdermal patch, spray, gum, and lozenges—and are equally effective for cessation.[37,38,197,198] NRTs stimulate the brain receptors targeted by nicotine, helping relieve nicotine withdrawal symptoms and cravings that lead to relapse.[37] Many people use NRT to help them get through the early stages of cessation, and those with more severe nicotine addiction can benefit from longer-term treatment. Use of NRT improves smoking cessation outcomes, and adding behavioral therapies further increases quit rates.[198] A combination of continual nicotine delivery through the transdermal patch and one other form of nicotine taken as needed (e.g., lozenge, gum, nasal spray, inhaler) has been found to be more effective at relieving withdrawal symptoms and cravings than a single type of NRT.[37,167,198] Researchers estimate that NRT increases quit rates by 50 to 70 percent.[37] Using the patch for up to 24 weeks has been shown to be safe.[39]



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**Bupropion**—Bupropion (immediate-release and extended-release) was originally approved as an

antidepressant. It works by inhibiting the reuptake of the brain chemicals norepinephrine and dopamine as well as stimulating their release. Bupropion has been found to increase quit rates compared with placebo in both short- and long-term follow-up studies[166,198,199] and is indicated for smoking cessation. It is equally effective to NRT.[167]

**Varenicline**—Varenicline helps reduce nicotine cravings by stimulating the alpha-4 beta-2 nicotinic receptor but to a lesser degree than nicotine. Varenicline boosts the odds of successfully quitting, compared with unassisted attempts.[198] Varenicline increased the likelihood of quitting compared with placebo, and some studies find that it is more effective than single forms of NRT[200,201] and bupropion.[167]

In a primary care setting, 44 percent of patients on varenicline, either alone or combined with counseling, were abstinent at the 2-year follow-up. Patients who participated in group therapy and adhered to the medication were more likely to remain abstinent.[202] Research also suggests that this medication may be more effective than bupropion.[199]

**Medication combinations**—Some studies suggest that combining NRT with other medications may facilitate cessation. For example, a meta-analysis found that a combination of varenicline and NRT (especially, providing a nicotine patch prior to cessation) was more effective than varenicline alone.[203] Similarly, adding bupropion to NRT also improved cessation rates.[199] For smokers who could not cut down significantly by using the NRT patch, combining extended-release bupropion and varenicline was more effective than placebo, particularly for men and those who were severely nicotine dependent.[139]

**Other antidepressants**—In addition to bupropion, some other antidepressant medications have also been found effective for smoking cessation, independent of their antidepressant effects, and are considered second-line treatments. A few small studies suggest that nortriptyline is equally effective as NRT.[167,199] Although nortriptyline may have side effects in some patients, the small studies for its use in smoking cessation have not reported any.[199] Researchers have not observed any impact of selective serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, and sertraline) on smoking, either alone or in combination with NRT.[199]

**Precision Medicine**—Researchers have been examining ways to personalize treatment based on important individual biological differences, including genetic differences. The field of pharmacogenetics examines how genes influence therapeutic response to medications, providing

critical information to help tailor pharmacotherapies to the individual for maximum benefit. For example, people metabolize nicotine at different rates because of variations in several genes. Individuals who metabolize nicotine quickly smoke more, show greater dependence, and have more difficulty quitting.[204] Such genetic variation influences the therapeutic responses to NRT and other cessation medications.[204,205] A recent study compared rates of abstinence 1 week after treatment for slow, normal, and fast metabolizers of nicotine who were randomly assigned to either placebo, NRT, or varenicline. Results indicated that varenicline worked best for normal nicotine metabolizers, whereas NRT patches were most effective for slow metabolizers.[205,206]

**Promising medications and ongoing research**—NIDA supports research to develop new and improve current treatment options for smoking cessation based on a growing understanding of the neurobiology of addiction. In the area of medications, research is focusing on the receptors targeted by nicotine and the brain circuits and regions known to influence nicotine consumption.[208] Newer brain targets—including the orexin and glutamate signaling systems—have also shown promise for medication treatment.[207,208] Repurposing medications already on the market for other indications may also prove useful in the search for new smoking cessation therapies.[209,210] This approach has been successful in the past, as bupropion was an established antidepressant before the FDA approved it as a smoking cessation medication. One current candidate is N-acetylcysteine, a medication for acetaminophen overdose, which has shown promise as a treatment for various substance use disorders—including nicotine dependence.[211] Another approach that could prevent relapse and that has shown promise in early studies is a nicotine vaccine, which would generate antibodies that keep nicotine from reaching the brain.[212,213]

## Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a relatively new approach being tested to treat addiction. It is a physiological intervention that noninvasively stimulates neural activity in targeted areas of the brain using magnetic fields. Multiple TMS pulses given consecutively are referred to as repetitive TMS (rTMS). The FDA has approved two rTMS devices for depression treatment in adults.

Research on rTMS as a treatment for smoking cessation is in early stages but has shown promise.[214,215]

Among adult smokers who had not been able to quit using other treatments, high-frequency TMS treatment significantly reduced the number of cigarettes smoked. Combining high-frequency TMS with exposure to smoking cues improved effectiveness and boosted the overall abstinence rate

to 44 percent at the end of the treatment. Six months after treatment, 33 percent of participants remained abstinent from cigarettes.[216] Future randomized controlled clinical trials with large numbers of patients will be needed to establish its efficacy for smoking cessation.

# How can we prevent tobacco use?

The medical consequences of tobacco use—including secondhand exposure—make tobacco control and smoking prevention crucial parts of any public health strategy. Since the first Surgeon General's Report on Smoking and Health in 1964, states and communities have made efforts to reduce initiation of smoking, decrease exposure to smoke, and increase cessation. Researchers estimate that these tobacco control efforts are associated with averting an estimated 8 million premature deaths and extending the average life expectancy of men by 2.3 years and of women by 1.6 years.[18] But there is a long way yet to go: roughly 5.6 million adolescents under age 18 are expected to die prematurely as a result of an illness related to smoking.[13]

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Prevention can take the form of policy-level measures, such as increased taxation of tobacco products; stricter laws (and enforcement of laws) regulating who can purchase tobacco products; how and where they can be purchased; where and when they can be used (i.e., smoke-free policies in restaurants, bars, and other public places); and restrictions on advertising and mandatory health warnings on packages. Over 100 studies have shown that higher taxes on cigarettes, for example, produce significant reductions in smoking, especially among youth and lower-income individuals.[217] Smoke-free workplace laws and restrictions on advertising have also shown benefits.[218]

Prevention can also take place at the school or community level. Merely educating potential smokers about the health risks has not proven effective.[218] Successful evidence-based interventions aim to reduce or delay initiation of smoking, alcohol use, and illicit drug use, and otherwise improve outcomes for children and teens by reducing or mitigating modifiable risk factors and bolstering protective factors. Risk factors for smoking include having family members or peers who smoke, being in a lower socioeconomic status, living in a neighborhood with high density of tobacco outlets, not participating in team sports, being exposed to smoking in movies, and being sensation-seeking.[219] Although older teens are more likely to smoke than younger teens, the earlier a person starts smoking or using any addictive substance, the more likely they are to develop an addiction. Males are also more likely to take up smoking in adolescence than females.

Some evidence-based interventions show lasting effects on reducing smoking initiation. For instance, communities utilizing the intervention-delivery system, Communities that Care (CTC) for students aged 10 to14 show sustained reduction in male cigarette initiation up to 9 years after the end of the intervention.[220]

# What research is being done on tobacco use?

New scientific developments can improve our understanding of nicotine addiction and spur the development of better prevention and treatment strategies.

## Genetics and Epigenetics

An estimated 50-75 percent of the risk for nicotine addiction is attributable to genetic factors.[221] A cluster of genes (CHRNA5-CHRNA3-CHRNB4) on chromosome 15 that encode the ?5, ?3, and ?4

protein subunits that make up the brain receptor for nicotine[221–223] are particularly implicated in nicotine dependence and smoking among people of European descent. Variation in the CHRNA5 gene influences the effectiveness of combination NRT, but not varenicline.[224] Other research has identified genes that influence nicotine metabolism and therefore, the number of cigarettes smoked,[225] responsiveness to medication,[204,205] and chances of successfully quitting.[226] For example, the therapeutic response to varenicline is associated with variants for the CHRNB2, CHRNA5, and CHRNA4 genes, while bupropion-related cessation is linked with variation in genes that affect nicotine metabolism.[227]

Smoking can also lead to persistent changes in gene expression (epigenetic changes), which may contribute to associated medical consequences over the long term, even following cessation.[228] Epigenetic changes may serve as a potential biomarker for prenatal tobacco smoke exposure. Researchers found tobacco-specific changes at 26 sites on the epigenome, and this pattern predicted prenatal exposure with 81 percent accuracy.[229] A large scale meta-analysis of data on epigenetic changes associated with prenatal exposure to cigarette smoke also identified many epigenetic changes that persisted into later childhood.[230] More research is needed to understand the long-term health impacts of these changes.

## Neuroimaging

Cutting-edge neuroimaging technologies have identified brain changes associated with nicotine dependence and smoking. Using functional magnetic resonance imaging (fMRI), scientists can visualize smokers' brains as they respond to cigarette-associated cues that can trigger craving and relapse.[231] Such research may lead to a biomarker for relapse risk and for monitoring treatment progress, as well as point to regions of the brain involved in the development of nicotine addiction.[29]

A neuroimaging technology called default-mode or resting-state fMRI (rs-fMRI) reveals intrinsic brain activity when people are alert but not performing a particular task. Using this technique, researchers are examining the neurobiological profile associated with withdrawal and how nicotine impacts cognition.[232] Comparisons between smokers and nonsmokers suggest that chronic nicotine may weaken connectivity within brain circuits involved in planning, paying attention, and behavioral control—possibly contributing to difficulty with quitting.[233] fMRI studies also reveal the impact of smoking cessation medications on the brain—particularly how they modulate the activity of different brain regions to alleviate withdrawal symptoms and reduce smoking. A review of these studies

suggested that NRT enhances cognition during withdrawal by modulating activity in default-network regions, but may not affect neural circuits associated with nicotine addiction.[234]

Some imaging techniques allow researchers to visualize neurotransmitters and their receptors, further informing our understanding of nicotine addiction and its treatment.[27] Using these techniques, researchers have established that smoking increases the number of brain receptors for nicotine. Individuals who show greater receptor upregulation are less likely to stop smoking.[28] Combining neuroimaging and genetics may yield particularly useful information for improving and tailoring treatment. For example, nonsmoking adolescents with a particular variant in the CHRNA5-CHRNA3-CHRNB4 gene cluster (which is associated with nicotine dependence and smoking) showed reduced brain activity in response to reward in the striatum as well as the orbitofrontal and anterior cingulate cortex. This finding suggests that genetics can influence how the brain processes rewards which may influence vulnerability to nicotine dependence.[235] Neuroimaging genetics also shows that other genes, including ones that influence dopamine neurotransmission, influence reward sensitivity and risk for addiction to nicotine.[236]

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# Where can I get further information about tobacco/nicotine?

To learn more about tobacco, nicotine, and other drugs of use and misuse, visit the NIDA website at www.drugabuse.gov or contact DrugPubs at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).

# NIDA's website includes:

- Information on drugs of use and misuse and related health consequences
- NIDA publications, news, and events
- Resources for health care professionals, educators, and patients and families
- Information on NIDA research studies and clinical trials
- Funding information (including program announcements and deadlines)
- International activities
- Links to related websites (access to websites of many other organizations in the field)
- Information in Spanish (en español)

# NIDA websites and webpages

- drugabuse.gov/publications/drugfacts/cigarettes-other-tobacco-products
- drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes
- drugabuse.gov
- teens.drugabuse.gov
- researchstudies.drugabuse.gov
- irp.drugabuse.gov

# For physician information

- NIDAMED: drugabuse.gov/nidamed

## Other websites

Information on nicotine/tobacco abuse is also available through the following websites:

- National Cancer Institute (NCI)
- Centers for Disease Control and Prevention (CDC)
- Substance Abuse and Mental Health Services Administration (SAMHSA)
- Monitoring the Future
- The Partnership for Drug-Free Kids